Message

From: Hill, Donna [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=314E939D15314E119BF60E95644293DB-HILL, DONNA]
Sent: 12/18/2018 3:05:52 PM
To: Ex. 6 Personal Privacy (PP) Chernoff, Neil [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=e2c8b0a1aa0347f7ab9245a7a5f28de1-Chernoff, Neil]
Subject: FW: EPA Perfluorates

Here's Elizabeth's answers.

From: Elizabeth Whitley <elizabeth@pathogenesisllc.com>
Sent: Monday, December 17, 2018 11:21 PM
To: Hill, Donna <Hill.Donna@epa.gov>
Subject: RE: EPA Perfluorates

Hi Donna,

So, answers to your three questions:

1) Does the increased mitosis in the 3mg/kg group indicate the prelim to hyperplasia, response to apoptosis, or something else?
    a. This question is why you didn't get a deeper discussion section in the report yet-I've been working on teasing out possible underlying mechanisms! :>) Here is what I think so far.
    b. There is evidence that perfluoroalkyls activate proliferator-activated receptor-α (PPARα), a nuclear transcription factor that regulates lipid metabolism and inflammation.
    c. PPARα activation in the liver results in hepatocellular hypertrophy and changes in lipid metabolism associated with increased smooth endoplasmic reticulum and proliferation of peroxisomes. (Pastoor, et al., 1987)
    d. Prolonged PPARα activation in rodents also induces hepatocyte proliferation that can progress to hepatocellular adenoma and carcinoma through a non-genotoxic mechanism.(Peters, Cattley, Gonzalez, 1997)
    e. The mechanism by which PPARα induces hepatocyte proliferation appears to involve downregulation of the microRNA let-7c gene which is an inhibitor of c-Myc. Down regulation of let-7c releases inhibition of c-Myc, resulting in hepatocyte proliferation.(Gonzalez and Shah, 2008)
    f. There are species differences in PPARα responsiveness, with mice being more sensitive than humans.(Gonzalez and Shah, 2008)
    g. Apparently, there may also be PPARα-independent mechanisms in play for some PFAs.
    h. So, I expect that a study with more animals would indicate differences in mitotic figures between groups at this duration (since I saw a few mitotic figures in the high dose) and a longer mouse study might result in hepatic tumorigenesis. Because of the species differences in PPARa responses, however, I'm not sure what implication for human health might be if you did demonstrate increased PPARα activity. I'll expand on this discussion and add several other references I have found.
2) Is the degree of apoptosis in the range of normal expected turnover?
    a. There were only small numbers of apoptotic cells and in regions that didn't make me worry about a compound effect. So, yes, I think it is within normal range for hepatocyte turnover.
3) The intracytoplasmic vacuoles you describe as being consistent with glycogen- is there something that makes you lean more towards glycogen than lipid?
    a. Some of the vacuoles look a lot like glycogen- lacy, indistinct edges. Some vacuoles, however, have more crisp edges and were easier to focus up and down on. Those I suspect may be lipid. I tried to decide on a means to score the vacuoles, but didn't come up with criteria that I thought would differentiate, given the hepatocyte hypertrophy.

b. If you have wet tissues still- even formalin-fixed liver- that can be cut for frozen sections, we could get an Oil Red O stain on the high dose and vehicle animals to get an estimate of lipid content.

And a very Merry Christmas to you and yours!

Elizabeth

From: Hill, Donna <Hill.Donna@epa.gov>
Sent: Monday, December 17, 2018 11:33 AM
To: Elizabeth Whitley <elizabeth@pathogenesisllc.com>
Subject: RE: EPA Perfluorates

Thank you Elizabeth! I have 3 questions about the data you sent.

1) Does the increased mitosis in the 3mg/kg group indicate the prelim to hyperplasia, response to apoptosis, or something else?
2) Is the degree of apoptosis in the range of normal expected turnover?
3) The intracytoplasmic vacuoles you describe as being consistent with glycogen- is there something that makes you lean more towards glycogen than lipid?

Thanks and no rush on the answer.

Merry Christmas!

Donna

From: Elizabeth Whitley <elizabeth@pathogenesisllc.com>
Sent: Monday, December 17, 2018 12:59 AM
To: Hill, Donna <Hill.Donna@epa.gov>; Chernoff, Neil <Chernoff.Neil@epa.gov>
Subject: RE: EPA Perfluorates

Hi Donna and Neil,
Attached please find a draft of my report on the Nafion byproduct-2 samples. I still want to do some more reading and expand the discussion some.

Please let me know if you have any questions or suggestions. We can discuss by phone, if that is most convenient for you.

I'm sorry it has taken longer than the few weeks I had anticipated.

Best regards,
Elizabeth

From: Hill, Donna <Hill.Donna@epa.gov>
Sent: Friday, December 14, 2018 9:45 AM
To: Elizabeth Whitley <elizabeth@pathogenesisllc.com>; Chernoff, Neil <Chernoff.Neil@epa.gov>
Subject: RE: EPA Perfluorates Pathogenesis SoW & Quote 102618.pdf

Hi Elizabeth,
Hope you are well and the holiday preparation is not too maddening. Neil and I are wondering where you are with evaluating the Nafion byproduct 2 livers? Don't worry about an official report, just checking in.

Thanks,
Donna

From: Elizabeth Whitley <elizabeth@pathogenesisllc.com>
Sent: Tuesday, October 30, 2018 11:34 AM
To: Chernoff, Neil <Chernoff.Neil@epa.gov>
Cc: Hill, Donna <Hill.Donna@epa.gov>
Subject: RE: EPA Perfluorates Pathogenesis SoW & Quote 102618.pdf

Hi Neil,
Thanks for these papers. This background really helps!

The tissues have arrived at the lab- I'll let you know as soon as I have them.

Best regards,
Elizabeth

From: Chernoff, Neil <Chernoff.Neil@epa.gov>
Sent: Friday, October 26, 2018 12:41 PM
To: Elizabeth Whitley <elizabeth@pathogenesisllc.com>
Cc: Hill, Donna <Hill.Donna@epa.gov>
Subject: RE: EPA Perfluorates Pathogenesis SoW & Quote 102618.pdf

Hi Elizabeth,

Likewise re: speaking with you. I'm attaching two reviews on PFAS, one general (ATSDR) and the other more specific (HESD), but much of what is true with PFOA also applies to NBP2 that we're working on.

Have a nice weekend.

Neil

From: Elizabeth Whitley [mailto:elizabeth@pathogenesisllc.com]
Sent: Friday, October 26, 2018 12:54 PM
To: Hill, Donna <Hill.Donna@epa.gov>; Chernoff, Neil <Chernoff.Neil@epa.gov>
Subject: EPA Perfluorates Pathogenesis SoW & Quote 102618.pdf

Hi Donna and Neil,
It was great to talk with you yesterday! Your perfluorates sound really nasty. I'm looking forward to seeing the histology after your description of the livers. Attached please find the statement of work and quote that we discussed. Please let me know if you have any questions.

When you are ready to ship the samples, please send them to: (and please let me know when you ship them and the tracking number)

Molecular Pathology Core Histology Laboratory
Attention: Lynda Schneider/DavdMachart
1395 Center Drive, Rm D11-41
University of Florida
Gainesville, FL 32610

Please include a list of the blocks as you did before. I'll fill out and send you (and them) the MPC submission form to cross coordinate. I am attaching a copy of my submission form, in case you didn't find a previous copy in your files. If you can direct me to any references on the possible toxic effects or mechanisms, that would be much appreciated, too!

Please let me know if you have any questions or other needs!

Hope your weekend is cool and crisp!

Best regards,
Elizabeth